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National variation in use of Immunosuppression for kidney transplantation: A call for evidence-based regimen selection

Running title: Variation in Maintenance Immunosuppression

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Abbreviations: ACR, Acute cellular rejection; AZA, Azathioprine; CNI, calcineurin inhibitor; CsA, Cyclosporine; CTG, chronic transplant glomerulopathy; EBE, Empirical Bayes Estimates; eGFR, estimated glomerular filtration rate; HRSA, Health Resources and Services Administration; ICC, intra-class correlation coefficient; ISx, Immunosuppression; MOR, median odds ratio; MPA/AZA, mycophenolate acid; mTOR, mammalian target of rapamycin; OPTN, Organ Procurement and Transplantation Network; PCD, pharmacy claims database; Pred, Prednisone; PTDM, post-transplant diabetes mellitus; RCT, randomized controlled trial; SRL, Sirolimus; Tac, Tacrolimus

ABSTRACT

Immunosuppression management in kidney transplantation has evolved to include an increasingly diverse choice of medications. While informed by patient and donor characteristics, choice of immunosuppression regimen varies widely across transplant programs. Using a novel database integrating national transplant registry and pharmacy fill records, immunosuppression use 6-12–and 12-24 months post-transplant was evaluated for 22,453 patients transplanted at 249 U.S. programs in 2005-2010. Use of triple immunosuppression comprising tacrolimus, mycophenolic acid or azathioprine, and steroids varied widely (0-100% of patients per program), as did use of steroid-sparing regimens (0-77%), in sirolimus-based regimens (0-100%) and cyclosporine-based regimens (0-78%). Use of triple therapy was more common in highly sensitized patients, women, and recipients with dialysis duration > 5 years. Sirolimus use appeared to diminish over the study period. Overall, patient and donor characteristics explained only a limited amount of the observed variation in regimen use, while center choice explained 30-46% of the use of non-triple therapy

immunosuppression. The majority of patients who received triple therapy (79%), cyclosporine-based (87.6%) and sirolimus-based regimens (84.3%) continued these regimens in the second year post-transplant. This population-based study of immunosuppression practice demonstrates substantial variation in center practice beyond that is explained by differences in patient and donor characteristics.

INTRODUCTION

Advances in immunosuppression (ISx) have substantially reduced the risk of early acute cellular rejection (ACR) in patients undergoing immunologically compatible kidney transplantation.(1) The incidence of ACR has declined despite an increased prevalence of highly sensitized patients, re-transplant recipients and the growing use of extended-criteria organs. Unfortunately, the marked reduction in ACR has come at the cost of rising rates of ISx-related complications including bacterial and viral infections (pneumonia, urinary tract infections, BK viruria), malignancy, and accelerated cardiovascular disease (2-5). Furthermore, long term survival remains limited by chronic transplant glomerulopathy (CTG), interstitial fibrosis/tubular atrophy, inflammation, and subclinical cellular and humoral rejection despite apparently effective ISx. (6, 7)

In addition to complications associated with a globally immunosuppressed state, specific agents have well described associations with metabolic and physiologic derangements. Tailoring immunosuppression based on patient characteristics, pharmacological side effects, and donor factors to balance these toxicities with the need to maintain effective and durable long-term ISx remains a key challenge for transplant professionals.(8-14) To develop an accurate assessment of current practices in the selection of maintenance ISx for kidney transplantation, we constructed a novel database integrating national transplant registry data with pharmacy fill records. Our primary goals were to examine associations of patient characteristics with regimen selection in a multi-level analytic framework and to quantify the contributions of center-level practice variation on ISx utilization.

METHODS

Data Sources

Study data were constructed by linking OPTN records a large U.S. pharmaceutical claims data (PCD) clearinghouse. The OPTN data system includes data on all donor, wait-listed candidates, and transplant recipients in the U.S., submitted by the members of the OPTN, and has been described elsewhere (15). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN contractor. The PCD comprises National Council for Prescription Drug Program 5.1-format prescription claims aggregated from multiple sources including data clearinghouses, retail pharmacies, and prescription benefit managers for approximately 60% of U.S. retail pharmacy transactions, including those reimbursed by private payers, public payers, and self-paid fills. After Institutional Review Board and HRSA approvals, PCD records from 2005 to 2010 were linked with OPTN records for kidney transplant recipients. Because of the large sample size, the anonymity of the patients studied, and the non-intrusive nature of the research, a waiver of informed consent was granted per the Department of Health and Human Services Code of Federal Regulations (Title 45, Part 46, Paragraph 46.116). Analyses were performed using Health Information Portability and Accountability Act (HIPAA) compliant limited datasets. This study was approved by the Institutional Review Board (IRB) of Saint Louis University.

Study Sample

Eligible transplant recipients had an OPTN kidney transplant record and pharmacy claims during months 6 to 12 post-transplantation to allow ISx regimen stabilization. A subset of the primary sample who also had PCD data 12-24 months post-transplant were examined in a secondary analysis. ISx regimens were classified using PCD data into 6 mutually exclusive groups: Group 1 (Reference): Standard triple therapy, defined as Tac with mycophenolic acid (mycophenolate mofetil, mycophenolate sodium), or azathioprine (MPA/AZA), and prednisone (Pred), "Tac+MPA/AZA+Pred"; Group 2: Corticosteroid-sparing, "Tac+MPA/AZA"; Group 3: MPA/AZA sparing, "Tac alone, Tac+Pred"; Group 4: mTOR-based, defined by any fill for Sirolimus (SRL) as the mTOR available in the study period, with or without other agents including CNI, "SRL-based"; Group 5: Cyclosporine (CsA)-based, defined by CsA without SRL, "CsA-based"; Group 6: "Other regimens" including CsA withdrawal, or other trial medications. Patients in groups 1-3 did not received SRL or CsA.

Analyses

Observed Variation in Regimen Use across Centers

To visually assess unadjusted variation in ISx regimen use at the center level across the U.S, the observed proportion of patients receiving each regimen was computed for each center and displayed as stacked bar plots.

Combined Center and Case-Level modeling

Bi-level hierarchical models were constructed to adjust for clustering effects: Level 1 comprised patient/donor and transplant (case) factors and Level 2 represented the center, wherein the use of each alternative regimen was compared individually to the reference regimen (pairwise). Empirical Bayes Estimates (EBE) provide the adjusted proportion (with 95% confidence intervals, CI) of use of a regimen of interest compared to the reference regimen, incorporating case-mix adjustment from the hierarchical model. If the 95% CI for a given center's EBE of use a regimen of interest does not include the median national rate of use, this indicates a prescribing pattern that is statistically significantly different from the expected rate of use for that regimen.

Heterogeneity in ISx prescribing across centers was quantified using intraclass correlation (ICC) and median odds ratios (MOR). ICC is defined as the ratio of cluster variance (center impact) to the total observed variance in ISx use, with contributions in our study framework defined as center-related, case-related, and other unmeasured impacts. In this context, the ICC quantifies the proportion of total variance in ISx use that is accounted for by center. The MOR provides the median of the odds that patients with identical characteristics will receive the ISx regimen of interest when 2 centers are drawn at random (performed for all possible pairs of centers). For example, a MOR of 2.0 means that if we select centers at random across all centers, then a patient with a given set of characteristics is, on an average, twice as likely to receive the ISx regimen of interest at one of the randomly selected center than at the other selected center (16). The adjusted odds ratios (aOR) of being placed on an ISx regimen other than standard triple therapy was determined for patient and donor factors, after accounting for the impact of center using the hierarchical model.

Secondary analyses were performed in the subgroup with available serum creatinine data at 6-months for computation of 6-mo estimated glomerular filtration rate (eGFR). Estimated GFR was computed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (17).

Data were analyzed using Stata 13, College Station, TX. Hierarchical logistic regression modeling was in Stata using the "xtmelogit" command with center as a random intercept. The ICC and the MOR were calculated using "xtmrho" (3rd party suite) command.

Contributions of Case-Level Factors to Variation in ISx Use

To quantify the degree that variance in ISx regimen use was explained by recipient and donor characteristics, we performed multivariate logistic regression modeling with ISx regimen as the dependent variable and case factors as the predictors. Pairwise models were constructed to assess the relative likelihood of utilizing each specific regimen (as outlined above) compared with standard triple drug therapy.

RESULTS

Integrated PCD and registry data were available for 22,453 transplants performed at 249 centers in the study period. The study sample included 27% of all transplants performed. Compared to transplant recipients registered in the OPTN who were not captured in the PCD, the proportion of patients with private insurance (44% vs. 39% P<.001) and Caucasian race (59% vs. 53% p<.001) was increased in the study cohort (**Table 1**). Overall, 7.7% of patients experienced a reported acute rejection in the first 6 months post-transplant. Triple therapy (Tac+MPA/AZA+Pred) was the most frequently used regimen (33.8% patients overall), followed by steroid-sparing (Tac+MPA/AZA) in 25.8%, MPA/AZA sparing (Tac alone, Tac+Pred) in 11.3%, SRL-based (with or without Tac/CSA) in 9.9%, and CSA-based in 7.8%; other regimens were filled in 11.6% of the sample. The majority of patients in the SRL group were also receiving CNIs (Tac 37.5%, CSA 15.3%). There was substantial variation in the unadjusted use of ISx regimens across centers (**Figure 1**). The use of triple ISx varied from 0-100% patients across transplant centers, steroid-sparing regimens (0-77%), SRL-based (0-100%), CSA-based (0-78%), and other (0-100%).

Patient -Level Correlates of ISx Regimen Use

Patient characteristics were strongly correlated with differential use of maintenance ISx regimens 6-12 months post-transplant (**Table 2**). Older patients were more likely to receive regimens without MPA/AZA than triple therapy: [age > 60 years (adjusted odds ratio [aOR] for MPA/AZA sparing: 1.50, p<0.0001), 49-60 years old (aOR 1.20, P<0.01]. Compared with use in adults age 31-45, CSA-based regimens were more commonly used in patients aged 49-60 years (aOR 1.43, p<0.0001) and especially in older patients >60 years (aOR 1.87, p<0.0001), and less likely to be used in younger adults 18-30 years (aOR 0.55, p<0.0001) and children aged <18 years old (aOR 0.42, p<0.0001).

Women were more likely to be maintained on triple ISx regimens than men. While ISx regimens were generally similar in African Americans compared with Caucasians, African Americans were less likely to receive CSA-based regimens (aOR 0.69, p<0.01). Obese patients were

less likely to receive Tac without MPA/AZA (aOR 0.85, p<0.05), or SRL-based therapies (aOR 0.84 p<.05).

Prolonged ESRD was also associated with a higher use of "other" ISx regimens (aOR 1.25, p<0.01). Compared to diabetic patients, patients with glomerulonephritis as the cause of their ESRD were more likely to receive triple therapy. There was also a trend for greater use of steroid-sparing ISx in patients with polycystic kidney disease (aOR 1.16, p=0.08).

As expected, patients at a higher immunological risk for ACR, including those with prior transplantation, increasing levels of HLA mismatch, and higher PRA, were less likely to receive regimens other than the reference triple therapy. For example, PRA >=80 was associated with less use of Tac+MPA/AZA (aOR 0.58, p<0.0001), Tac alone, Tac+Pred (aOR 0.80, p<0.04), SRL-based (aOR 0.61, p<0.0001), CSA-based (aOR 0.51, P<0.0001), or other (aOR 0.77, P<0.01) regimens. Induction therapy with depleting agents was associated with a higher use of steroid-sparing, MPA/AZA-sparing, and SRL-based regimens, while induction with IL-2R was associated with a statistically lower likelihood of receiving steroid-sparing and antimetabolite-sparing regimens.

Over time, there have been alterations in the ISx landscape which may in part reflect changes in case characteristics. There was decreasing use of SRL use compared to reference ISx regimen (2006 vs 2005: aOR 0.53, p<0.0001; 2009 vs 2005: aOR 0.29, p<0.0001). Compared to recipients of transplants from standard criteria donors, recipients from living-related donors appear to have higher rates of receiving steroid-sparing regimens, Tac+MPA/AZA (aOR 1.34, p<0.0001), while recipients from ECD donors were more likely to receive SRL-based regimens (aOR 1.73, p<0.0001). ISx regimen did not vary by donor race except that there was an increased use of "Tac alone, Tac+Pred" in recipients from "Other" race donors (aOR 1.27, p <0.01). Economic factors appeared to influence prescription patterns with cash payers appearing more likely to be taking "minimized" regimens, eg: Tac+MPA/AZA (aOR 1.43, p<0.0001); MPA/AZA-sparing (aOR 1.73, p<0.0001) and Other (aOR 1.69, p<0.0001) regimens. Patients with a history of acute rejection in the first 6mo were less likely to receive a steroid-sparing (aOR 0.39, P<0.0001) or CsA-based (aOR 0.64, P<0.01) regimen, subsequently, during mos 6-12 after transplant.

Associations between patient and donor characteristics and regimen choice during months 6-12 post-transplant were also examined after adjusting for eGFR at 6 months in the sample with available data for eGFR computation (n=12,340). There were no changes in inferences across patient level characteristics. However, there was an association of SRL use with eGFR, such that SRL use was less common (aOR 0.69, p<0.0001) among patients with an eGFR >60 (vs. ref 30-60

ml/min/1.73 m2) but more increasingly common with lower eGFR 15-30 (aOR 2.84, p<0.0001) and < 15 ml/min/1.73 m2 (aOR 3.28, p<0.01).

Temporal Trends

Among the subset of the primary sample who also had PCD data 12-24 months post-transplant (n=18,298), regimen selection in the second year was compared with the regimen at 6-12 months. Compared with initial regimen at 6-12 months, the proportion of patients on triple therapy increased from 33.8% to 37.7% in year two post-transplant (**Table S1**). The majority of patients who received triple therapy (79%), CSA-based (87.6%) and SRL-based regimens (84.3%) continued these regimens in second year post-transplant (**Table S2**). By comparison, only 55.8% of those on "other" regimens at year 1 remained on other regimens during year 2.

Center-Driven Variation in Regimen Use

Hierarchical logistic regression models demonstrated that between-center variation in use of specific ISx regimens was significantly greater than what would be expected based on differences in patient demographics or transplant characteristics (p<0.0001). Based on EBE comparing the relative use of a specific alternative ISx regimens to triple therapy in two-way analyses, we identified 28% of centers in which frequency of Tac+MPA/AZA use was statistically higher than expected while 13% employed Tac alone, Tac+Pred at higher rates. (**Table 3A**). Addition of 6-month eGFR in the model in secondary analysis reduced the variation in practice among centers (**Table 3B**). In the fully adjusted model, including eGFR at 6 months, 20.1% of centers prescribed Tac+MPA/AZA at rates significantly greater than expected. Similarly, 19.6% of centers had statistically significantly greater use of SRL and 20.3 % of centers were higher than expected users of CSA-based regimens.

Finally, the degree of heterogeneity in prescribing practice was assessed using the ICC. The ICCs for SRL, CSA and Tac+MPA/AZA regimens in models unadjusted for patient and donor characteristics were 0.40, 0.46 and 0.30 respectively, which supports that 40%, 46% and 30% of the variation in the use of the "non-standard" regimens was due to "center effect" (**Table 4**). The ICCs remained similar even after adjustment for case factors. These ICC did not change over time when the sample was stratified into two eras. The MORs from case-factor adjusted models for each regimen compared with reference triple therapy ranged from 2.08 to 5.15. (**Table 4**). Thus, a patient with a given set of characteristics was, on average, 4.4-times as likely to receive a SRL-based regimen as triple therapy, at specific centers.

DISCUSSION

Using a novel linkage of the national transplant registry data and a large pharmaceutical claims database, we identified substantial variation in the choice of maintenance ISx regimen after kidney transplantation. Nationally, over one third of patients received triple maintenance ISx 6-12 months post-transplant. However, in some centers, 100% of patients, regardless of characteristics, were placed on triple therapy, whereas other centers used this regimen rarely if ever. After adjustment of patient and donor characteristics, ISx use varied markedly across centers, with 2- to 5-fold variation in the likelihood of use of non-triple therapy based regimens.

Although case-level factors are a weaker determinant of regimen choice than center practice, we identified a number of clinically rational associations between ISx regimen selection and patient and donor characteristics. Patients with increased immunological risk (glomerulonephritis, high PRA, re-transplant) were all more likely to be maintained on triple therapy. In contrast, patients with lower eGFRs at 6 months were much more likely to be placed on a renal-sparing regimen containing SRL. CsA use appears to be common in a selected group of centers, with average variation of 5-fold in expected use across centers after accounting for patient and donor characteristics. Likelihood of use of CsA-based and SRL-based regimens declined markedly over the study period

These data provide the first rigorous assessment of ISx regimen with appropriate sample size to identify the effect of center practice on utilization after controlling for donor, recipient, and transplant characteristics. Examination of this unique database demonstrates marked variation in center practice even after adjusting for factors including the use of induction agents, living donation, race and ethnicity. In one prior examination of center level variation in the use of corticosteroids, Fu et al. examined utilization and outcomes from OPTN records. At the time of their publication (2008), approximately one-third of recipients were discharged on a steroid sparing regimen. Interestingly, the selective use of steroid-free regimen appeared more effective. Compared to centers from which 100% of patients were discharged on a steroid free regiment, centers in which only 20-49% of patients were discharged steroid-free had fewer deaths (OR 0.73) and graft failures (OR 0.71). Outcomes at these centers, however, were better than outcomes at centers that discharged all patients on triple therapy. This study suggests that tailored use of non-reference ISx regimens may improve patient outcomes.(18, 19)

In contrast with prior studies of ISx use reported to the OPTN, the current study is based on pharmacy fill records which are more comprehensive than center-reported transplant registry data

at intermittent survey points. The use of pharmacy claims to assess ISx regimens has been previously validated based on comparisons to electronic medical records and the OPTN registry. While the concordance between all three data sources was excellent at one year for CNIs (99-100%), the claims were somewhat more accurate in determining the use of MMF and AZA.(20, 21) Comparison of a large electronic pharmacy claims database with written prescriptions found negligible error rates of 0.02% for drug dispensed (22). Lau, et al. (23) and Boethius, et al. (24) independently found pharmacy records and claims to have near-perfect agreement with home inventories. However, physician-directed dose changes that are communicated without written prescriptions will be missed. Further, while the absence of pharmacy claim for any drug is interpreted as no use in this design, alternative explanations may include noncompliance of use from an uncaptured "over-supply". Our study database also lacked drug levels as a measure of drug exposure. Although nothing is more accurate than an audit of patients' households (25), such data collection is expensive, intrusive, and difficult to accomplish on a large scale.

Our study was limited to the regimens used at in the first_2 years post-transplant. It is certainly possible that ISx management may be changed after the second post-transplant anniversary; however, the majority of the early conversation trials (e.g. Spare the Nephron) recommend conversion within the first year and late corticosteroid withdrawal has been associated with higher rates of rejection than early withdrawal (26). In the current study, regimen selection remained stable between years 1 and 2 in the majority of patients, especially those on triple therapy, SRL-based, and CsA-based regimens.

Clearly, there are also clinical conditions that are not captured in OPTN data that impact the choice of ISx after kidney transplant. For example, patients with a history of CNI-induced thrombotic microangiopathy, severe CNI neurotoxicty or nephrotoxicity may be more likely to receive SRL-based therapy. As supported by our findings, early acute rejection episodes may result in increased intensity of ISx. Patients receiving ISx through trials rather than pharmacy fills also cannot be identified through our study data, although some of the patients in the "other" category were likely managed under study protocols. Finally, the years of data collection in our study ended in 2010, and ongoing research is needed to evaluate the use and trends of recently approved agents including extended-dose tacrolimus, everolimus, and belatacept.

In conclusion, we found that despite an increasing body of literature which informs the tailoring of ISx therapy on the basis of patient characteristics, ISx choice remains largely driven by center practice. Overall, clinically expected patient and donor characteristics were associated with ISx choice (e.g. highly-sensitized patients were more commonly treated with triple therapy);

however, case factors explained less than 6% of the national variation in practice in our study. Center choice explains up to nearly half of observed variation in regimen use. Further research including collaborative clinical trials and secondary data analyses of contemporary practice are needed to determine the relationship between center practice, post-transplant outcome, and patient selection to advance from a "one size fits all" to a personalized medicine approach to ISx.

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Disclaimer

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Figure Legends

Figure 1: Proportion of patients receiving one of six mutually exclusive immunosuppression regimens during months 6-12 post-transplant. Each horizontal bar represents an individual center within US regions ordered by the proportion of patients that received triple ISx (Tac + MPA/AZA + Pred—

shown in orange). Overall percentage of regimen use at patient-level across centers: Tac+MPA/AZA+Pred, 33.8%; Tac+MPA/AZA (No Pred), 25.8%; Tac without MPA/AZA, 11.3%; SRL-based, 9.9%; CSA-based, 7.8%; and other regimens, 11.6%. CSA, Cyclosporine; ISx, immunosuppression; MPA/AZA, mycophenolate acid; Pred, prednisone; Tac, tacrolimus.

Figure 2: Empirical Bayes Estimates for likelihood of regimen use compared with reference regimen. Red bar demonstrates national average rate of use of each regimen (within pair-wise regimen comparisons). Each red dot represents adjusted use at one center and the blue bars reflect 95% confidence intervals (CI) for use at the center determined by Empirical Bayes Estimates, adjusting for case factors of recipients at the center; exclusion of the national average by a 95% CI reflects adjusted center use significantly above or below the national average.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Comparison of immunosuppression regimens 6-12 months post-transplant and 12-24 months post-transplant.

Table S2. ISx regimen selection in the second year compared with the regimen at 6-12 months, among patients with complete data (N=18,298). ISx, immunosuppression.

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Figure 1.

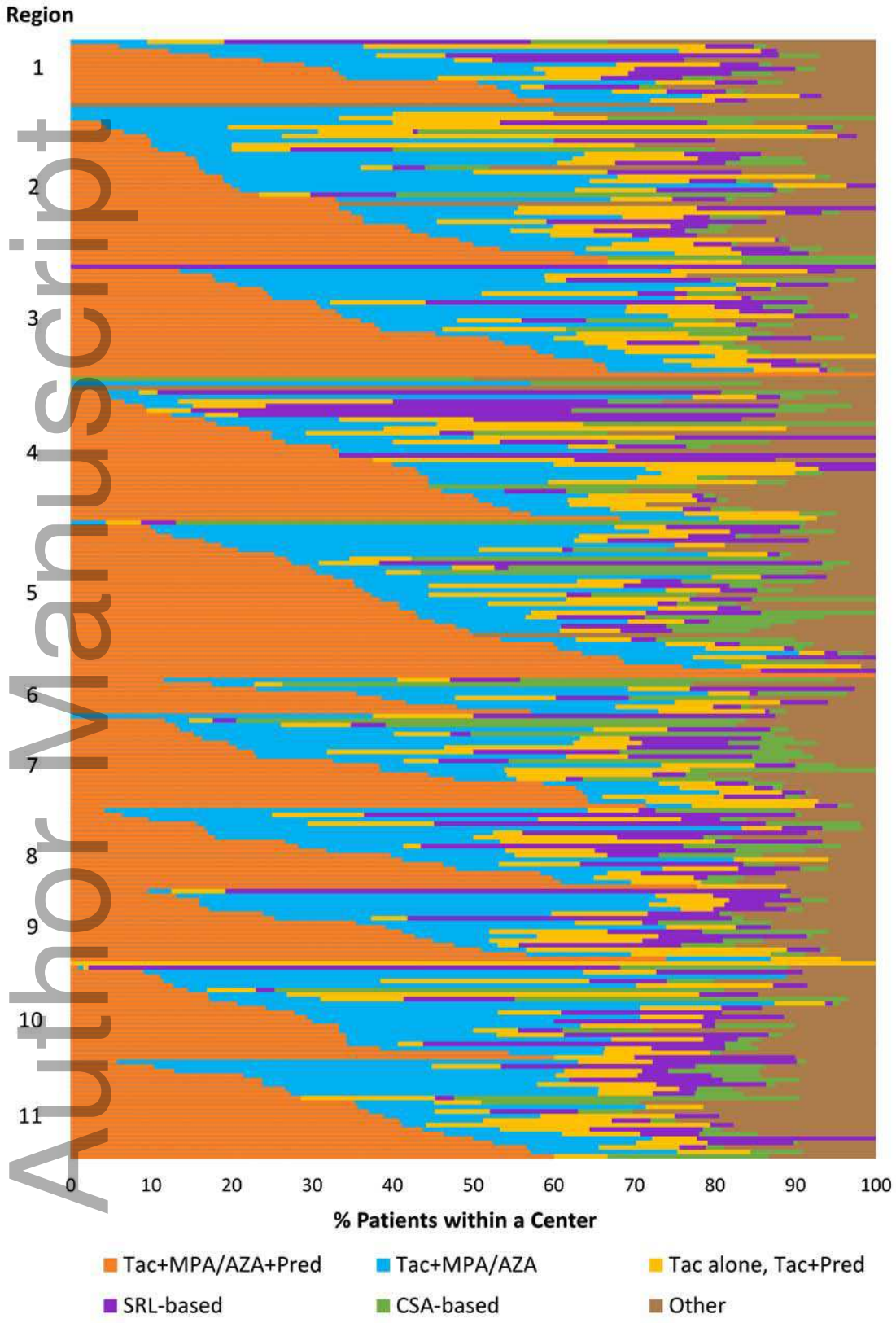

Figure 2.

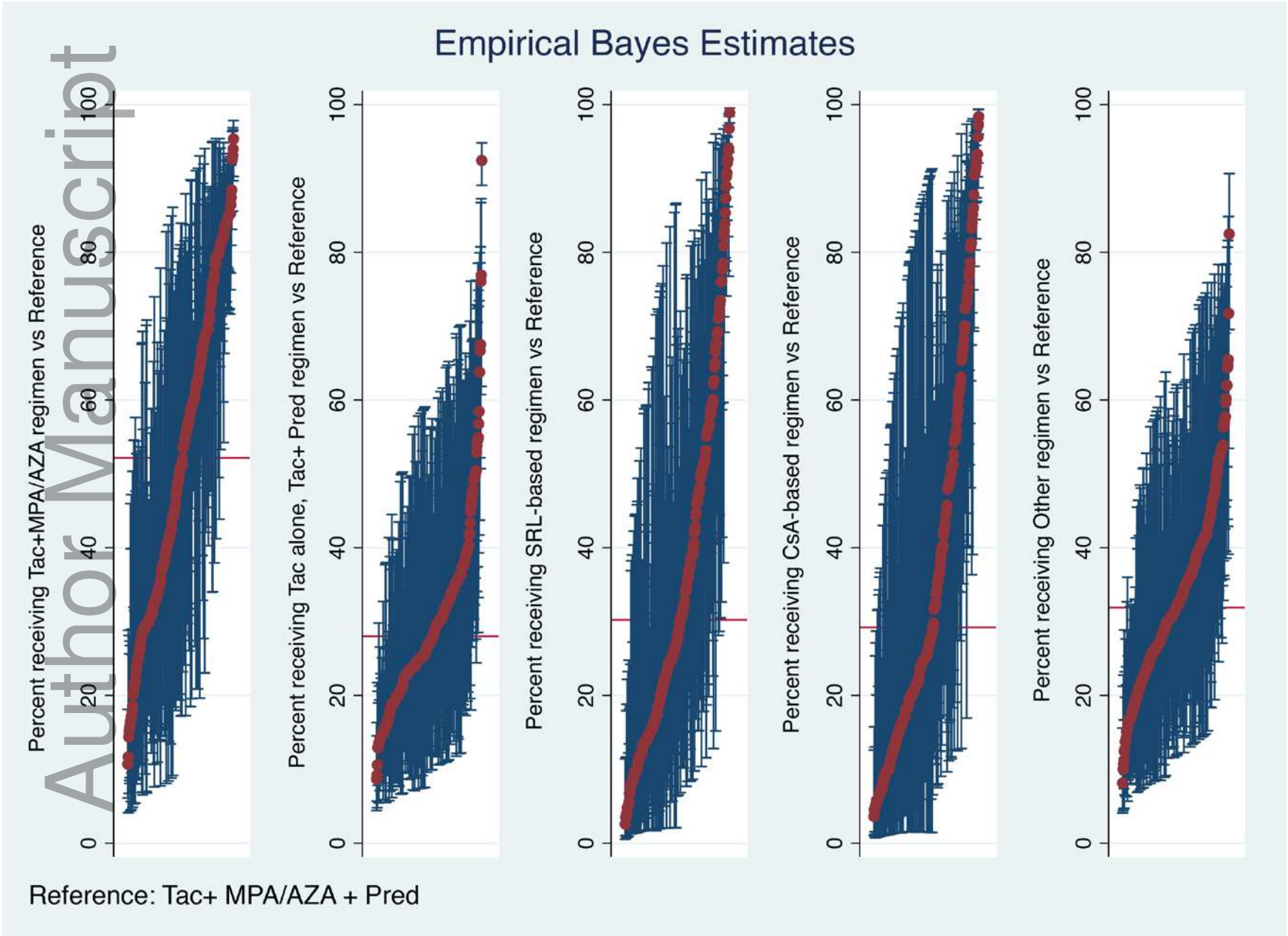

Table 1. Comparison of donor and recipient characteristics from patient in the pharmacy claims data sample (PCD Study Sample) and OPTN patients not included in the sample

Candidate/Donor Characteristics	PCD Study Sample (N=22,453)	Other OPTN Registrants (N=61,109)
	%	%
Recipient age (years)		‡
<18	5.47	4.9
18 to 30	9.4	9.32
31 to 45	21.77	21.22
46 to 59	38.69	37.53
>=60	24.68	27.04
Gender		*
Male	60.13	61.11
Female	39.87	38.89
Recipient race		‡
White	59.06	52.97
African American	22.08	25.36
Other	18.86	21.67
ESRD duration		‡
None (pre-emptive)	19.33	17.45
>0 to 24 months	33.43	31.04
25 to 60 months	28.87	30.82
>60 months	16.67	19.1
Missing	1.69	1.59
Body Mass Index, kg/m2		‡
<18.5	5.1	4.54
18.5 to 25	33.08	32.64
25 to 30	32.14	32.4
>30	29.04	29.44
Missing	0.65	0.97
Cause of ESRD		‡
Diabetes	21.61	22.75

Glomerulonephritis	21.2	21.09
Hypertension	20.94	22.53
Polycystic kidney disease	9.39	8.66
Other	26.86	24.97
Recipient Comorbidities		‡
Diabetes	30.85	32.45
Hypertension	53.92	52.16‡
Coronary disease/angina	3.59	3.52
COPD	0.98	0.95
Cerebral vascular disease	1.87	1.65*
Peripheral vascular disease	3.8	3.56
Highest level of education		†
Grade school	6.55	6.9
High school	38.08	38.17
Some college or higher	38.94	39.61
Unknown	16.43	15.32

Table 1, continued. Comparison of donor and recipient characteristics from patient in the pharmacy claims data sample (PCD Study Sample) and OPTN patients not included in the sample

Employment status		‡
Working	29.98	28.15
Not working	52.03	55.64
Unknown	17.98	16.21
Insurance type		‡
Public	56.02	60.58
Private	43.80	38.94
Other/unknown	0.17	0.47
Previous transplant		*
Yes	13.12	13.76
No	86.88	86.24
Peak PRA level		‡
<10	70.27	68.04
10 to 79	17.64	18.63

>=80	7.9	8.05
Missing	4.19	5.28
HLA mismatches		†
Zero A, B, and DR	10.47	9.9
Zero DR	46.32	45.79
Other	43.21	44.31
Transplant year		‡
2005	19.49	19.81
2006	22.46	19.72
2007	22.4	18.99
2008	20.22	19.61
2009	15.43	21.87
Donor race		‡
White	71.05	68.26
Black	12.42	13.26
Other	16.54	18.48
Donor Gender		
Male	52.51	53.09
Female	47.49	46.91
CMV sero-pairing		‡
Recipient-, Donor-	17.2	15.55
Recipient+, Donor-	21.57	21.82
Recipient-, Donor+	17.39	16.96
Recipient+, Donor+	37	38.72
Not reported	6.84	6.95
Donor type		‡
Standard criteria deceased	50.51	53.13
Expanded criteria deceased	9.38	10.22
Living related	24.55	22.08
Living unrelated	15.56	14.57

P-values: * P 0.02–0.04; † P 0.0001–0.01; ‡ P < 0.0001

COPD, chronic obstructive pulmonary disease; CMV, cytomegalovirus; ESRD, end-stage renal disease; OPTN, Organ Procurement and Transplantation Network; PCD, pharmacy claims database; PRA, panel-reactive antibody.

Table 2. Association of recipient and donor characteristics with immunosuppression regimen from multi-level model including center effects for ISx regimen vs. reference regimen (Tacrolimus+MPA/AZA+Prednisone)

	Tac+MPA/AZA	Tac alone, Tac+Pred	SRL-based	CSA-based	Other
	aOR (95% CI)				
Age Group					
<18	0.67 (0.52-0.86)†	1.13 (0.84-1.52)	0.77 (0.53-1.13)	0.42 (0.27-0.66)‡	0.70 (0.52-0.95)*
18-30	0.91 (0.78-1.07)	0.89 (0.72-1.10)	0.98 (0.77-1.24)	0.55 (0.40-0.74)‡	0.90 (0.74-1.09)
31-45	Reference	Reference	Reference		Reference
46-59	1.06 (0.95-1.19)	1.20 (1.04-1.39) †	1.11 (0.94-1.31)	1.43(1.19-1.71) ‡	1.16 (1.02-1.33)*
>=60	1.09 (0.96-1.25)	1.50 (1.28-1.76) ‡	1.12 (0.93-1.37)	1.87 (1.53-2.30) ‡	1.10(0.95-1.29)
Female	0.98 (0.90-1.07)	0.87 (0.78-0.97) †	0.90 (0.79-1.03)	0.93 (0.81-1.07)	0.93 (0.84-1.03)
Race Group					
White	Reference	Reference	Reference	Reference	Reference
Black	0.90 (0.80-1.03)	1.00 (0.86-1.17)	0.98 (0.82-1.17)	0.69 (0.56-0.86)†	0.93 (0.80-1.07)
Other	0.93 (0.81-1.06)	0.91 (0.77-1.07)	0.76 (0.62-0.94) †	0.98 (0.80-1.21)	0.91 (0.78-1.07)
Cause of ESRD					
Diabetes	Reference	Reference	Reference	Reference	Reference
Glomerulonephritis	0.80 (0.70-0.92)†	0.82 (0.69-0.97)*	1.03 (0.84-1.26)	0.97 (0.79-1.19)	0.88 (0.75-1.02)
Hypertension	0.96 (0.84-1.10)	0.90 (0.77-1.06)	1.21 (0.99-1.48)	0.98 (0.80-1.21)	0.99 (0.85-1.15)
Polycystic kidney Disease	1.16 (0.98-1.37)	1.00 (0.81-1.23)	1.23 (0.96-1.59)	0.98 (0.75-1.28)	0.95 (0.78-1.16)
Other	0.98 (0.86-1.12)	0.99 (0.84-1.16)	1.21 (0.98-1.48)	0.92 (0.74-1.14)	0.99 (0.85-1.16)

Previous kidney transplant	0.49 (0.41-0.56)‡	0.74 (0.63-0.88)†	0.81 (0.67-0.99)*	0.61 (0.48-0.77)‡	0.81 (0.69-0.99)†
ESRD duration					
None	1.04 (0.92-1.17)	1.14 (0.98-1.32)	1.18 (0.99-1.41)	0.95 (0.78-1.17)	1.12 (0.97-1.29)
0-24	Reference	Reference	Reference	Reference	Reference
25-60	0.95 (0.85-1.06)	0.97 (0.84-1.12)	1.05 (0.89-1.25)	0.94 (0.78-1.13)	1.12 (0.98-1.28)
>60	0.87 (0.75-1.00)	1.06 (0.89-1.26)	1.17 (0.95-1.43)	1.13 (0.91-1.42)	1.25(1.06-1.47)†
Missing	1.01 (0.73-1.40)	1.17 (0.80-1.71)	1.30 (0.83-2.06)	1.16 (0.69-1.95)	1.06 (0.72-1.59)
HLA mismatches					
Zero A, B, and DR	Reference	Reference	Reference	Reference	Reference
Zero DR	0.69 (0.60-0.80)‡	0.96 (0.79-1.16)	0.76(0.61-0.95)*	0.67 (0.53-0.83)‡	0.74 (0.62-0.87)‡

Table 2, continued. Association of recipient and donor characteristics with immunosuppression regimen from multi-level model including center effects for ISx regimen vs. reference regimen (Tacrolimus+MPA/AZA+Prednisone)

Other	0.69(0.60-0.80)‡	1.04 (0.86-1.26)	0.83(0.67-1.04)	0.65 (0.52-0.82)‡	0.78 (0.66-0.92)†
Peak PRA level					
<10	Reference	Reference	Reference	Reference	Reference
10-79	0.84 (0.75-0.94)†	0.92 (0.80-1.06)	0.95 (0.80-1.12)	0.91 (0.76-1.10)	0.86 (0.75-0.99)*
>=80	0.58 (0.49-0.70)‡	0.80 (0.65-0.99)*	0.61(0.47-0.78)‡	0.51(0.38-0.69)‡	0.77 (0.63-0.93)†
Missing	0.99 (0.78-1.27)	0.82 (0.60-1.11)	0.58 (0.39-0.87)†	0.89 (0.59-1.34)	0.80 (0.59-1.09)
BMI					
Under weight	1.12 (0.92-1.38)	1.03 (0.80-1.32)	0.82 (0.59-1.12)	1.20 (0.85-1.68)	0.97 (0.75-1.26)
Normal weight	Reference	Reference	Reference	Reference	Reference
Over weight	1.00 (0.90-1.12)	0.90 (0.79-1.03)	0.93 (0.80-1.08)	1.02 (0.87-1.20)	1.05 (0.93-1.18)
Obese	0.96 (0.87-1.08)	0.85 (0.74-0.97)*	0.84 (0.71-0.99)*	0.98 (0.82-1.16)	1.02 (0.90-1.16)

Missing	0.96 (0.59-1.56)	0.85 (0.46-1.58)	0.65 (0.27-1.60)	0.72 (0.28-1.84)	0.92 (0.52-1.62)
Hypertension	1.03 (0.93-1.14)	0.91 (0.80-1.03)	0.95 (0.81-1.10)	0.98 (0.83-1.15)	0.90 (0.80-1.01)
Highest level of education					
Grade school	1.04 (0.86-1.26)	0.94 (0.74-1.19)	0.87 (0.65-1.16)	0.92 (0.68-1.23)	0.88 (0.69-1.12)
High school	0.96 (0.87-1.05)	0.87 (0.77-0.98)*	1.00 (0.86-1.15)	0.98 (0.83-1.14)	1.02 (0.91-1.14)
College & higher	Reference	Reference	Reference	Reference	Reference
Unknown	0.98 (0.86-1.13)	0.99 (0.84-1.17)	1.08 (0.89-1.33)	0.91 (0.73-1.14)	1.20(1.02-1.40)*
Transplant year					
2005	Reference	Reference	Reference	Reference	Reference
2006	0.85 (0.74-0.97)*	0.83 (0.71-0.97)*	0.53 (0.44-0.63)‡	0.56 (0.46-0.67)‡	0.86 (0.74-0.99)*
2007	0.86 (0.75-0.98)*	0.72 (0.61-0.85)‡	0.35 (0.29-0.42)‡	0.44 (0.36-0.54)‡	0.73 (0.62-0.85)
2008	0.97 (0.84-1.12)	0.87 (0.73-1.03)	0.31 (0.25-0.39)‡	0.40 (0.32-0.50)‡	0.85 (0.72-1.00)
2009	0.97 (0.83-1.14)	0.92 (0.76-1.11)	0.29 (0.23-0.37)‡	0.34 (0.26-0.44)‡	0.98(0.82-1.17)
Female Donor	0.94 (0.86-1.02)	1.03 (0.93-1.14)	1.05 (0.93-1.19)	0.97 (0.85-1.11)	1. 01(0.92-1.12)
Donor type					
SCD	Reference	Reference	Reference	Reference	Reference
ECD	0.88 (0.75-1.03)	1.12 (0.94-1.34)	1.73 (1.40-2.13)‡	0.94 (0.74-1.18)	1.17 (0.98-1.40)
LRD	1.34 (1.19-1.51)‡	0.89 (0.77-1.03)	1.16 (0.98-1.39)	0.98 (0.81-1.19)	1.11 (0.97-1.28)
LUD	1.01 (0.89-1.17)	0.86 (0.73-1.01)	0.95 (0.78-1.17)	0.75(0.60-0.94)†	0.99 (0.84-1.15)

Table 2, continued. Association of recipient and donor characteristics with immunosuppression regimen from multi-level model including center effects for ISx regimen vs. reference regimen (Tacrolimus+MPA/AZA+Prednisone)

Donor race					
White	Reference	Reference	Reference	Reference	Reference
Black	0.98 (0.85-1.13)	1.07 (0.90-1.26)	0.96 (0.78-1.17)	1.06 (0.83-1.35)	1.01 (0.86-1.19)
Other	1.01 (0.89-1.15)	1.27 (1.09-1.48)†	0.89 (0.73-1.08)	1.07 (0.88-1.31)	1.00 (0.86-1.16)
Pharmacy Payer					
Cash	1.43 (1.18-1.74)‡	1.73 (1.37-2.20)‡	1.11 (0.82-1.50)	1.00 (0.75-1.33)	1.69 (1.36-2.09)‡
Medicaid	1.18 (0.98-1.42)	0.92 (0.73-1.17)	0.75 (0.57-0.99)*	0.91 (0.67-1.25)	0.70 (0.54-0.91)†
Third Party	1.07 (0.97-1.18)	1.34 (1.19-1.51)‡	1.13 (0.98-1.30)	1.03 (0.88-1.21)	1.25 (1.12-1.40)‡
Induction depletion	1.42(1.26-1.60)‡	1.23(1.07-1.42)†	1.21(1.01-1.45)*	0.88(0.73-1.07)	1.01 (0.88-1.16)
Induction IL2R	0.83(0.73-0.96)†	0.85(0.72-0.99)*	1.13(0.93-1.37)	1.05(0.85-1.29)	1.21(1.05-1.41)†
Acute Rejection	0.39 (0.32-0.47) ‡	0.92 (0.76-1.11)	1.09 (0.88-1.35)	0.64(0.49-0.83) †	1.08 (0.91-1.28)

P-values: * P 0.02–0.04; † P 0.0001–0.01; ‡ P < 0.0001

Table 3A. Center Level Empirical Bayes Estimates adjusted for case-level characteristics.*

ISx Regimen (Ref: Tac+ MPA/AZA +Pred	No. of centers in pairwise comparison	No. of centers significantly above reference probability	No. of centers significantly below reference probability
Tac+MPA/AZA	244	68 (27.9%)	60 (24.6%)
Tac alone, Tac+Pred	243	31 (12.8%)	27 (11.1%)
SRL-based	241	61 (25.3%)	33 (13.7%)
CSA-based	242	64 (26.4%)	19 (7.9%)
Other	246	33 (13.4%)	31 (12.6%)

*Constructed from pairwise comparisons of regimen of interest versus reference regimen (Tac+MPA/AZA+Pred)
CSA, Cyclosporine; ISx, immunosuppression; MPA/AZA, mycophenolate acid; Pred, prednisone; Tac, tacrolimus.

Table 3B. Center Level Empirical Bayes Estimates adjusted for case-level characteristics including 6-month eGFR

ISx Regimen (Ref: Tac+ MPA/AZA+Pred	No. of centers in pairwise comparison	No. of centers significantly above reference probability	No. of centers significantly below reference probability
Tac+MPA/AZA	239	48 (20.1%)	39 (16.3%)
Tac alone, Tac+Pred	238	17 (7.1%)	18 (7.6%)
SRL-based	240	47 (19.6%)	18 (7.5%)
CSA-based	236	48 (20.3%)	11 (4.7%)
Other	240	18 (7.5%)	16 (6.7%)

*Constructed from pairwise comparisons of regimen of interest versus reference regimen (Tac+MPA/AZA+Pred)
CSA, Cyclosporine; ISx, immunosuppression; MPA/AZA, mycophenolate acid; Pred, prednisone; Tac, tacrolimus.

Table 4. Heterogeneity across unadjusted and both adjusted models.

ISx Regimen (Ref: Tac+ MPA/AZA+Pred)	Proportion of variance in hierarchical model explained by center characteristics (Unadjusted)	MOR	Proportion of variance in hierarchical model explained by center, adjusted for donor/recipient factors	MOR	Proportion of variance in model explained by donor/recipient characteristics
Tac+MPA/AZA	0.30	3.11	0.30	3.14	0.05
Tac alone, Tac+Pred	0.16	2.10	0.15	2.08	0.04
SRL-based	0.40	4.16	0.42	4.42	0.04
CSA-based	0.46	5.02	0.47	5.15	0.06
Other	0.14	2.03	0.15	2.06	0.02

Proportion of variance in hierarchical model is equal to the Intraclass Correlation Coefficient, ICC.
MOR, Median Odds Ratio

CSA, Cyclosporine; ISx, immunosuppression; MPA/AZA, mycophenolate acid; Pred, prednisone; Tac, tacrolimus.